HC and LO Appendix - Advancing Male Contraception

Capstone Project

Contents

LO Appendix

LO: #geneidentification

Description of the LO from the course syllabus: Design experiments to identify candidate causative genes and genetic variants.

What is a "4" level application of this LO as described in the course? A **4-level** application of this LO requires more than identifying candidate genes; it necessitates an in-depth mechanistic evaluation of their roles, validation through experimental techniques, and a clear connection to biological pathways. Strong applications will analyze knockout studies, gene expression profiling, and functional assays to determine gene impact on a phenotype, rather than merely listing genes implicated in a pathway.

What would be a "4" level application of this LO in THIS project? For this capstone review, a **4-level** application of #geneidentification involves not just listing genes implicated in spermatogenesis but deeply analyzing their function within the **retinoic acid (RA) signaling pathway**. This requires evaluating knockout and overexpression studies that establish causality, discussing how genetic variants in genes such as *Stra8*, *Kit*, and *ALDH1A2* affect RA metabolism, and integrating findings from pharmacogenomic studies that link these genes to non-hormonal contraceptive targets. Additionally, assessing how YCT-529 interacts with these pathways adds another dimension of applied genetic analysis.

Where is this LO applied in this project? This LO is applied in both the **main review paper** and the **appendices**.

- **Main Review Paper: Retinoic Acid Metabolism and Spermatogenesis**, where I explore the role of *ALDH1A2* and *RDH10* in synthesizing bioactive RA and regulating spermatogonial differentiation.
- **Main Review Paper: Gene Regulation in the Spermatogenic Cycle**, where I discuss the downstream effects of RA-induced genes such as *Stra8* and *NANOS2* in meiotic initiation.
- **Appendices: Targeting Retinoic Acid Pathways for Contraception**, where I expand on the pharmacological relevance of gene modulation via RA inhibition.

How have I applied this LO in this project? Application 1 (Main Review Paper): Identifying RA Biosynthesis Genes as Gatekeepers of Spermatogenesis In **Retinoic Acid Metabolism and Spermatogenesis**, I analyzed how *ALDH1A2* and *RDH10* regulate RA availability for germ cell differentiation. Using gene knockout models, I showed that loss of *ALDH1A2* leads to meiotic failure, emphasizing its role as a bottleneck enzyme in RA synthesis. To further refine this application, I incorporated studies where RA biosynthesis inhibitors were used, reinforcing how targeting these genes can modulate RA availability for contraception.

Application 2 (Main Review Paper + Appendices): Spermatogonial Differentiation and the Role of *Stra8* and *Kit* In **Gene Regulation in the Spermatogenic Cycle**, I examined the transcriptional activation of *Stra8* by RA and how its knockout in mice prevents germ cells from entering meiosis. I extended this analysis by integrating studies on *Kit*, a downstream effector essential for spermatogonial proliferation. My analysis in the **appendices** further contextualizes these findings by evaluating pharmacological approaches to modulating *Stra8* expression in drug-based male contraception.

Application 3 (Appendices): Linking YCT-529's Mechanism to RA-Dependent Gene Expression In **Targeting Retinoic Acid Pathways for Contraception** (Appendices), I connected YCT-529's inhibitory effects to transcriptional repression of RA-responsive genes. I specifically analyzed how YCT-529 affects the expression of *Stra8*, *Kit*, and *NANOS2*, demonstrating how modulating these genes could serve as an effective contraceptive strategy. By referencing pharmacokinetic studies, I established a framework for linking small-molecule inhibitors to gene regulatory mechanisms.

Each of these applications provides a comprehensive, experimental-grounded understanding of gene function in RA signaling, ensuring a **4-level** mastery of #geneidentification.

LO: #generegulationmechanisms

Description of the LO from the course syllabus: Distinguish between mechanisms to regulate the expression of genes. Cells employ various mechanisms to control protein and gene product levels. Regulation occurs at multiple stages: from transcription initiation to the stability and activity of gene products. In eukaryotes, alternative splicing enables a single gene to yield multiple distinct products. Gene expression regulation allows genetically identical cells to perform distinct functions across cell types, developmental stages, and environmental conditions. Regulation is often combinatorial, involving cis- and trans-acting factors, positive and negative control mechanisms, and complex interactions that shape expression patterns.

What is a "4" level application of this LO as described in the course? A **4-level** application extends beyond identifying gene regulation mechanisms to analyzing how they respond to specific stimuli and interact at multiple control levels. In previous coursework, a strong application of this LO involved mapping transcriptional repression in the *trp* operon under high tryptophan conditions and demonstrating how trans-acting factors fine-tune repression. Similarly, earning a 4 in previous problem sets required explaining how cis-acting elements like promoter mutations disrupt regulatory cascades, affecting transcription factor binding and downstream gene expression.

What would be a "5" level application of this LO in THIS project? A **5-level** application in this project requires going beyond conventional transcriptional control and integrating multiple regulatory mechanisms across different biological layers. This includes analyzing how **retinoic acid (RA) signaling controls spermatogenic gene expression at transcriptional, post-transcriptional, and epigenetic levels**, incorporating **miRNA-mediated gene silencing, histone modifications, and enhancer-promoter interactions**. Additionally, it requires distinguishing between **direct and indirect regulation**—for example, showing how RA's activation of *Stra8* is a direct effect of RARE binding, while its repression of *NANOS2* is mediated through downstream Sertoli cell signaling. A novel approach would be to **contextualize these regulatory mechanisms within pharmacological modulation**, proposing how YCT-529 might interfere with RA-mediated gene expression to suppress spermatogenesis selectively.

Where is this LO applied in this project? This LO is applied in both the **main review paper** and **appendices**:

- **Main Review Paper: Retinoic Acid and Spermatogenesis**, where I explore the transcriptional activation of *Stra8*, *Kit*, and *NANOS2* by RA, distinguishing its direct and indirect regulatory effects.
- **Main Review Paper: Post-Transcriptional Regulation in Germ Cells**, which details miRNA interactions with RA-responsive genes and how they fine-tune gene expression for controlled sperm maturation.
- **Appendices: Pharmacological Disruption of Retinoic Acid Signaling**, where I propose how YCT-529 could modulate epigenetic markers or interfere with RARE-binding transcription factors to alter gene expression.

How have I applied this LO in this project? Application 1 (Main Review Paper): RA-Dependent Transcriptional Regulation of Spermatogenesis In

Retinoic Acid and Spermatogenesis, I analyzed RA's role in activating *Stra8*, *Kit*, and *NANOS2* through its interaction with RAR/RXR nuclear receptors. I distinguished between **RA-responsive enhancer elements (RAREs)**, which drive direct transcriptional activation, and secondary regulatory networks like Sertoli cell-secreted GDNF that indirectly modulate germ cell differentiation. By mapping these interactions, I demonstrated how RA orchestrates spermatogenic gene expression at a systems level.

Application 2 (Main Review Paper): miRNA-Mediated Post-Transcriptional Control in Spermatogenesis In **Post-Transcriptional Regulation in Germ Cells**, I examined the role of *miR-202* and *miR-34c* in repressing RA target genes, controlling the timing of meiotic initiation. I integrated findings from gene knockdown studies, showing how loss of *miR-202* leads to premature differentiation. This analysis distinguished RA's role as a transcriptional activator from its indirect modulation through miRNA-driven fine-tuning.

Application 3 (Appendices): YCT-529 and Pharmacological Modulation of RA-Dependent Epigenetic Marks In **Pharmacological Disruption of Retinoic Acid Signaling** (Appendices), I extended my analysis to propose how YCT-529 might influence gene regulation epigenetically. I reviewed studies on histone acetylation at RA-responsive promoters and speculated that YCT-529 could suppress *Stra8* by disrupting H3K27 acetylation, effectively blocking transcriptional activation. This perspective aligns pharmacological inhibition with gene regulation mechanisms, showing how small molecules can modulate gene expression at multiple levels.

Consideration for a 5-Level Application This application extends beyond standard interpretations of gene regulation by **proposing a novel mechanistic link between YCT-529 and epigenetic modulation of spermatogenesis**. Most studies discuss RA as a transcriptional activator, but I explore how it interacts with **chromatin-modifying enzymes and non-coding RNAs to fine-tune gene expression over developmental timescales**. Additionally, I integrate **pharmacological perspectives**, bridging molecular biology with potential clinical applications. These elements go beyond coursework expectations, making a strong case for a 5-level application.

LO: #ns144-development

Description of the LO from the course syllabus: Analyze effects of spatially and temporally regulated differential gene expression in multicellular organisms. Developmental genetics explores how multicellular organisms progress from a fertilized egg to a complex organism, focusing on gene roles in development and how spatially and temporally regulated gene expression produces structures and functions. This process

can be influenced by cellular interactions and emergent properties, with gene expression patterns affecting development and leading to unique phenotypes. Techniques include forward genetics (#geneidentification) and reverse genetics, often using the "Find It, Lose It, Move It" approach.

What is a "4" level application of this LO as described in the course? A **4-level** application requires demonstrating a deep understanding of how altering gene expression spatially or temporally affects developmental outcomes. A strong application involves detailing how spatial gradients, morphogen concentration, or stage-specific gene activation influence cellular differentiation and tissue patterning. In a previous assignment, earning a 4 involved explaining how misregulation of *Pax6* during early eye formation alters tissue identity and induces ectopic eye structures. This required not just identifying key genes but explaining how their activation timing and spatial restriction drive distinct developmental fates.

What would be a "4" level application of this LO in THIS project? For this project, a **4-level** application involves examining how retinoic acid (RA) acts as a spatially and temporally regulated signal governing spermatogenesis. RA functions as a developmental cue that initiates transcriptional programs controlling meiotic entry and differentiation. A strong application would analyze how **RA gradients coordinate the activation of genes like** *Stra8*, *Kit*, and *NANOS2* at precise developmental windows, ensuring proper germ cell maturation. Additionally, it would explore how RA's effects vary across spermatogenic stages and cellular microenvironments, shaping differentiation in a position-dependent manner.

Where is this LO applied in this project? This LO is applied in:

- **Main Review Paper: Retinoic Acid's Role in Spermatogenesis**, where I analyzed how RA drives the spatial and temporal activation of genes critical for germ cell development.
- **Main Review Paper: Developmental Coordination in Germ Cell Maturation**, where I examined how RA-dependent gene regulation ensures synchronous progression of spermatogenic waves.
- **Appendices: Gene Regulation in Spermatogenesis**, where I extended my analysis by discussing how RA-responsive enhancers fine-tune gene expression dynamics.

How have I applied this LO in this project? Application 1 (Main Review Paper): RA as a Spatial and Temporal Regulator In **Retinoic Acid's Role in Spermatogenesis**, I mapped how RA gradients establish distinct spermatogenic phases, ensuring that genes like *Stra8* and *Kit* activate at the right time and location. I analyzed how differential RA distribution maintains spermatogonial stem cell renewal in some regions while driving differentiation in others, demonstrating the role of spatially restricted morphogen signaling.

Application 2 (Main Review Paper): RA-Driven Developmental Synchronization In **Developmental Coordination in Germ Cell Maturation**, I examined how the temporal release of RA pulses ensures synchronized spermatogenic progression. I highlighted how cyclic fluctuations in RA concentration regulate the transition between undifferentiated spermatogonia and preleptotene spermatocytes, allowing coordinated germ cell development.

Application 3 (Appendices): Enhancer-Mediated RA Response in Gene Regulation In **Gene Regulation in Spermatogenesis**, I extended my discussion by exploring how RA-responsive enhancers fine-tune transcriptional dynamics. I explained how RA binds RAR/RXR complexes to activate enhancer elements that modulate stage-specific gene expression, ensuring precise developmental control.

Evaluation of Application Strength This application demonstrates a **4-level mastery** by integrating multiple layers of gene regulation—RA as a morphogen, its cyclic fluctuations, and its enhancer-mediated effects—to explain how spatiotemporal gene control directs spermatogenesis. By detailing how RA gradients shape developmental trajectories across different germ cell populations, I have provided a mechanistically rich analysis that meets the expectations of this LO at a high level.

LO: #ns113-structuresandproperties

Description of the LO from the course syllabus: Apply principles of chemistry to analyze the structure and/or properties of atoms and molecules. This LO requires understanding how molecular geometry, bonding, and electronic distribution influence polarity, stability, reactivity, and solubility. Integrating chemical principles to explain how molecular features affect function and behavior in various contexts is key.

What is a "4" level application of this LO as described in the course? A **4-level** application demonstrates a thorough understanding of how molecular structure determines chemical properties and the ability to explain this clearly. Previously, I earned a 4 by drawing accurate Lewis structures, indicating bond polarities, assessing

resonance contributors for stability, and relating structural features to solubility patterns. For instance, analyzing resonance in the lactate ion and connecting it to bond length uniformity exemplified the clarity and depth expected at a 4-level application.

What would be a "4" level application of this LO in THIS project? In this project, a **4-level** application of #ns113-structuresandproperties involves a detailed analysis of YCT-529's molecular structure and its pharmacokinetic properties. A strong application would examine how the **chromene core** contributes to **lipophilicity and membrane permeability**, how the **benzoic acid moiety** facilitates **hydrogen bonding with RAR-α**, and how the **2,2-dimethyl substitutions** increase metabolic stability by preventing enzymatic oxidation. Additionally, I would discuss how the compound's **rigid fused-ring system** reduces conformational flexibility, improving target specificity by restricting non-specific protein interactions.

Where is this LO applied in this project? This LO is applied in:

- **Main Review Paper: Molecular Structure and Binding Affinity of YCT-529**, where I analyzed how structural features contribute to YCT-529's selective RAR-α inhibition.
- **Appendices: ADMET Predictions of YCT-529**, where I evaluated how molecular properties influence pharmacokinetic parameters such as solubility, permeability, and metabolic clearance.
- **Appendices: Lipophilicity and Drug Transport**, where I explored how the compound's high logP value enhances passive diffusion across biological membranes.

How have I applied this LO in this project? Application 1 (Main Review Paper): YCT-529's Binding Affinity and Molecular Interactions In **Molecular Structure and Binding Affinity of YCT-529**, I analyzed how **hydrogen bonding, van der Waals interactions, and π-stacking** stabilize YCT-529's binding to RAR-α. By detailing the interaction of the benzoic acid moiety with key residues in the ligand-binding domain, I demonstrated how these structural features drive high selectivity.

Application 2 (Appendices): ADMET Predictions and Chemical Properties In **ADMET Predictions of YCT-529**, I explored how the **chromene core and 2,2-dimethyl substitutions** contribute to metabolic stability by reducing susceptibility to CYP-mediated oxidation. Additionally, I connected the drug's **polar surface area (PSA)** to its **moderate oral bioavailability**, balancing solubility and permeability.

Application 3 (Appendices): Lipophilicity and Passive Membrane Diffusion In **Lipophilicity and Drug Transport**, I examined how YCT-529's **high logP value** enhances **cell membrane permeability** while also contributing to **plasma protein binding**, influencing both drug distribution and clearance rates.

Evaluation of Application Strength This application meets the criteria for a **4-level mastery** by clearly linking molecular structure to drug function and pharmacokinetics. By integrating **hydrogen bonding, lipophilicity, metabolic stability, and membrane permeability**, I provided a mechanistically rich discussion of how YCT-529's molecular architecture dictates its biological behavior.

LO: #ns164-molecularmechanism

Description of the LO from the course syllabus: Explain how a molecule or set of molecules influences a phenotype; explain the genetic, molecular, cellular, or physiological basis of a property of health, disease, or an agricultural or industrial application. This LO emphasizes understanding the specific molecular interactions that result in observable changes at the cellular or physiological level. It involves connecting molecular structure to function, detailing how these structures influence health or disease outcomes, or contribute to industrial applications.

What is a "4" level application of this LO as described in the course? A **4-level** application requires a precise and mechanistic explanation of how molecular interactions drive cellular or physiological effects. In a previous assignment on drug discovery, I earned a 4 by describing how Chloroquine's protonation enhances its affinity for heme within red blood cells (RBCs), preventing malaria parasites from detoxifying heme. This level of molecular insight exemplifies how structural properties translate to therapeutic action—key for achieving a **4-level** application.

What would be a "4" level application of this LO in THIS project? In this project, a **4-level** application of #ns164-molecularmechanism requires a detailed mechanistic analysis of how YCT-529's antagonistic action on **RAR-α** alters gene transcription and spermatogenesis. This includes describing YCT-529's structural features that facilitate its high-affinity binding to **RAR-α**, blocking normal ligand interactions with retinoic acid (RA). By detailing how this inhibition disrupts **coactivator recruitment, histone modification, and transcriptional activation**, I illustrate how molecular antagonism alters gene expression and, consequently, spermatogenesis.

Where is this LO applied in this project? This LO is applied in:

- **Main Review Paper: Retinoic Acid Receptor Antagonism and Gene Regulation**, where I analyzed YCT-529's molecular interaction with **RAR-α** and its downstream effects on spermatogenesis.
- **Appendices: Structural Insights into RAR-α Binding**, where I examined how YCT-529's chemical features affect receptor binding and transcriptional repression.
- **Appendices: Comparative Analysis of Retinoid Signaling Disruption**, where I compared YCT-529's mechanism with that of other RAR antagonists to contextualize its specificity.

How have I applied this LO in this project? Application 1 (Main Review Paper): YCT-529's Interaction with RAR-α and Its Effects on Gene Expression In **Retinoic Acid Receptor Antagonism and Gene Regulation**, I provided a stepwise molecular explanation of how YCT-529's binding to **RAR-α** prevents RA-dependent gene transcription. By **blocking coactivator recruitment** and stabilizing **corepressor complexes**, YCT-529 suppresses histone acetylation and chromatin relaxation, reducing the expression of *Stra8* and *Kit*, genes essential for meiosis initiation.

Application 2 (Appendices): Structural Insights into RAR-α Binding In **Structural Insights into RAR-α Binding**, I analyzed how YCT-529's **chromene core, hydrogen-bond donors, and lipophilic interactions** contribute to its high receptor affinity. By discussing its binding thermodynamics and comparing it to native RA, I demonstrated how molecular interactions dictate inhibitory potency and specificity.

Application 3 (Appendices): Comparative Analysis of Retinoid Signaling Disruption In **Comparative Analysis of Retinoid Signaling Disruption**, I contrasted YCT-529 with other RAR antagonists to contextualize its selectivity. This included evaluating how modifications in receptor-ligand interactions affect spermatogenesis and how structural alterations in synthetic analogs could improve pharmacological outcomes.

Evaluation of Application Strength This application meets the criteria for a **4-level mastery** by integrating **molecular structure, gene expression regulation, and physiological consequences**. By demonstrating how YCT-529's antagonism at **RAR-α** propagates through regulatory networks to influence spermatogenesis, I provided a mechanistically rich discussion that fully satisfies the objectives of #ns164-molecularmechanism.

HC Appendix

HC: #thesis

Description of Application: I formulated a clear, concise, and arguable thesis that positions YCT-529 as a transformative non-hormonal male contraceptive. The thesis integrates pharmacokinetics, receptor selectivity, and societal impact, ensuring logical coherence throughout the review.

What is a "4" level application of this HC? A **4-level application** requires the thesis to be **precise, substantial, and serve as the organizing principle** of the argument. It must effectively structure the discussion, guiding the flow of evidence and sub-arguments.

How have I applied this HC in this project? Application 1: A Focused, Arguable Central Claim The thesis asserts YCT-529's **RAR-α selectivity, metabolic stability, and non-hormonal mechanism**, shaping the discussion on its pharmacological potential.

Application 2: Structuring the Argument By outlining key themes—**molecular interactions, receptor binding, and pharmacokinetics**—the thesis ensures coherence, linking each section seamlessly.

Application 3: Refining Placement for Clarity Based on feedback, I relocated the thesis to the appendix, preserving the review's structural integrity while maintaining accessibility.

Evaluation of Application Strength This application meets **4-level criteria** by ensuring a **concise, substantial, and structurally integral thesis**, effectively guiding the paper's logical progression.

HC: #rightproblem

Description of Application: I carefully characterized the issue of male contraception by defining the **initial state** (inequities in contraception and high rates of unintended pregnancies), the **goal state** (developing an effective non-hormonal male contraceptive), and the **obstacles** (biological, pharmacokinetic, and societal barriers). This structured problem characterization ensures that the review paper remains focused on the necessity of YCT-529 as a targeted solution.

What is a "4" level application of this HC? A **4-level application** involves specifying the problem's scope, identifying obstacles, and ensuring a clear logical flow from problem characterization to proposed solutions.

How have I applied this HC in this project? Application 1: Defining the Problem Scope In the introduction, I outlined the lack of male contraceptive options, emphasizing the biological and societal need for YCT-529.

Application 2: Connecting Scientific and Social Barriers I discussed pharmacokinetic constraints (e.g., oral bioavailability, metabolic stability) and framed them within the broader context of contraceptive accessibility.

Application 3: Ensuring Logical Progression By structuring the review around these defined obstacles, I maintained a clear progression from problem statement to evaluating YCT-529's potential.

Evaluation of Application Strength This application meets **4-level criteria** by providing a well-reasoned and structured problem characterization, effectively guiding the review's focus and argumentation.

HC: #psychologicalexplanation

Description of the HC from the course syllabus: Analyze the interacting factors across levels of analysis that explain and shape the behavior of complex agents. Human behavior arises from multiple interacting factors, including biological, cognitive, social, and cultural influences. Understanding these interactions allows for a deeper analysis of individual and collective decision-making, biases, and responses to interventions.

What is a "4" level application of this HC? A **4-level application** requires integrating psychological theories to explain behavior at multiple levels, using empirical evidence to support claims, and demonstrating how cognitive, social, and biological mechanisms interact to shape decision-making.

What would be a "4" level application of this HC in THIS project? A strong application of #psychologicalexplanation in this review involves explaining the psychological barriers to male contraceptive adoption using behavioral science principles. This includes examining hormonal manipulation's cognitive and emotional effects, analyzing how societal norms influence decision-making, and discussing strategies to promote contraceptive uptake through behavioral interventions.

Where is this HC applied in this project? This HC is applied in the sections on **barriers to male contraceptive adoption** and **Advantages, Limitations, and Future Directions in Condom Use**. It also appears in discussions on **YCT-529's potential advantages** as a non-hormonal alternative and in the broader analysis of behavioral factors shaping contraceptive use.

How have I applied this HC in this project? Application 1: Psychological Resistance to Hormonal Male Contraceptives I explored how hormonal alterations impact mood, libido, and emotional regulation, leading to perceived identity shifts that deter men from hormonal options. Cognitive dissonance theory explains why men may rationalize avoiding hormonal contraception despite its benefits.

Application 2: Behavioral Decision-Making and Risk Perception I applied prospect theory to analyze how men disproportionately weigh uncertain side effects over long-term contraceptive benefits, explaining why mild perceived risks significantly reduce adoption rates.

Application 3: Condom Use and Cognitive Biases in Sexual Decision-Making In the **Advantages, Limitations, and Future Directions in Condom Use** section, I examined cognitive errors in condom use, such as impulsive decision-making in high-arousal situations, referencing the **health belief model** to explain how perceived risks and benefits shape usage behavior.

Application 4: Social Norms, Behavioral Interventions, and Choice Architecture By incorporating the **theory of planned behavior**, I analyzed how societal stigmas and cultural norms influence attitudes toward contraception. Additionally, I discussed **choice architecture** and behavioral interventions that promote non-hormonal contraceptive adoption, emphasizing how incentives and framing effects normalize shared contraceptive responsibility.

Evaluation of Application Strength This application meets the **4-level criteria** by integrating psychological theories across cognitive, behavioral, and societal levels. By linking contraceptive hesitancy to psychological mechanisms and proposing behavioral strategies to enhance uptake, I provided a well-supported, multidimensional analysis that exemplifies a strong application of #psychologicalexplanation.

HC: #breakitdown

Description of the HC from the course syllabus: Organize problems into tractable components and design solutions. Many complex issues are best addressed by breaking

them into subproblems, identifying relevant components, and structuring them in a way that facilitates problem-solving.

What is a "4" level application of this HC? A **4-level application** involves systematically segmenting a problem into meaningful subproblems and explaining their relevance. Strong applications not only categorize elements effectively but also justify why this breakdown improves clarity and problem-solving.

What would be a "4" level application of this HC in THIS project? In this project, a 4-level application means deconstructing male contraceptive development into distinct, manageable components—biochemical pathways, spermatogenesis regulation, and pharmacological interventions. This ensures that each section builds logically on the next, guiding the reader through YCT-529's scientific and societal relevance.

Where is this HC applied in this project? This HC is used in the **Introduction** to define the contraceptive problem, in **Section 2** when discussing RA signaling and spermatogenesis, and in the **Contraceptive Equity Discussion** to structure biological and societal considerations separately.

How have I applied this HC in this project? Application 1: Breaking Down Spermatogenesis into Key Stages In **Section 2**, I decomposed spermatogenesis into differentiation, meiosis, and spermiogenesis, explaining how retinoic acid influences each stage.

Application 2: Segmenting the Biochemical Basis of RA Signaling RA metabolism was broken into synthesis, degradation, and receptor activation, ensuring a clear stepwise understanding of its role in gene expression.

Application 3: Structuring the Contraceptive Equity Discussion I separated biological and societal factors, first addressing the limitations of existing male contraceptives, then proposing YCT-529's role as a solution.

Evaluation of Application Strength This structured approach improves readability and analytical depth, demonstrating a strong **4-level** application of #breakitdown by clarifying complex scientific and social issues into logical, actionable components.

HC: #complexcausality

Description of the HC from the course syllabus: Identify ways that multiple causes interact to produce complex effects. This HC requires analyzing how multiple

factors—biological, social, and systemic—combine to shape outcomes, including causal chains, necessary vs. sufficient conditions, and feedback loops.

What is a "4" level application of this HC as described in the course? A 4-level application requires not just identifying multiple causes but also explaining their interactions, such as reinforcing and balancing feedback loops. Strong applications use structured causal reasoning, detailing how distinct variables influence one another over time.

What would be a "4" level application of this HC in THIS project? In this paper, **complex causality** is applied by analyzing how biological, psychological, and societal factors shape contraceptive development and adoption. For instance, hormonal and non-hormonal contraceptives produce different side effects, influencing public perception and gendered contraceptive responsibility. Additionally, a **positive feedback loop** emerges: as men take on greater contraceptive responsibility, societal acceptance increases, reinforcing demand and reducing gender imbalances in reproductive healthcare.

Where is this HC applied in your project? This HC is primarily applied in **Sections 2 and 4**, where I discuss contraceptive adoption, social influences, and the biological mechanisms of sperm inhibition.

How have I applied this HC in this project? I applied this HC by mapping the historical bias toward female contraception, linking it to the limited funding for male contraceptive research. In addition, I examined biochemical pathways regulating sperm production, connecting molecular interactions to systemic outcomes. Finally, I explored how behavioral psychology impacts contraceptive decisions, demonstrating how these factors collectively shape contraceptive accessibility. This structured approach aligns with a **4-level** application by integrating multiple causal pathways into a cohesive explanatory framework.

HC: #ethicalconsiderations

Description of the HC from the course syllabus: Identify ethical considerations relevant to a situation or decision and explain them by appealing to values and/or ethical theory. This HC involves assessing fairness, justice, autonomy, and societal impact when making ethical judgments.

What is a "4" level application of this HC as described in the course? A 4-level application requires identifying ethical concerns, justifying them with ethical principles, and demonstrating their real-world implications. Strong applications analyze multiple perspectives and use established ethical frameworks.

What would be a "4" level application of this HC in THIS project? In this paper, I applied **ethical considerations** by analyzing the need for safer male contraceptives through fairness, autonomy, and reproductive justice. I discussed how the burden of contraception disproportionately falls on women, raising ethical concerns about equity in reproductive healthcare. The development of non-hormonal male contraceptives, such as YCT-529, is framed as a step toward shared responsibility and gender equality in contraception.

Where is this HC applied in your project? This HC is central to **the Background Information section**, where I explore ethical implications in male contraception, and in discussions on healthcare accessibility and individual choice.

How have I applied this HC in this project? I highlighted ethical challenges of hormonal contraceptives, emphasizing their side effects and the moral responsibility of expanding safer alternatives. Additionally, I examined the ethical duty of medical innovation to align with individual autonomy and diverse contraceptive needs. By integrating ethical principles such as justice and bodily autonomy, I presented a balanced, well-reasoned case for male contraceptive development. This structured ethical analysis demonstrates a strong **4-level** application by integrating fairness, accessibility, and societal implications.

HC: #shapingbehavior

Description of the HC from the course syllabus: Analyze how incentives, disincentives, and choice architecture influence the behavior of agents in a complex system and utilize them to interact effectively in social systems.

What is a "4" level application of this HC as described in the course? A **4-level application** requires a deep understanding of behavioral influence mechanisms, such as incentives, choice architecture, and feedback loops. It should go beyond listing influences by critically assessing their effectiveness and demonstrating how they can be used to promote behavioral change in a specific context.

What would be a "4" level application of this HC in THIS project? In this project, a **4-level application** of **#shapingbehavior** involves analyzing how behavioral incentives and systemic interventions can promote the adoption of male contraceptives. This includes evaluating how choice architecture in healthcare settings, public awareness campaigns, and social framing influence male participation in contraception.

Where is this HC applied in your project? This HC is applied in **the Background Information section**, where I discuss the societal reluctance toward male contraceptive use and explore strategies to shift behaviors toward greater acceptance.

How have I applied this HC in this project? I applied **#shapingbehavior** by examining how **incentives and choice architecture** influence men's willingness to use non-hormonal contraceptives. I highlighted how shifting contraceptive responsibility from solely women to men requires targeted interventions, such as emphasizing the reduced side effects of non-hormonal options and framing male contraception as a relational benefit that strengthens shared decision-making in family planning.

In the discussion of **healthcare interventions**, I analyzed how adjusting clinical interactions can guide behavior. For example, I suggested that presenting male contraceptive options **during routine healthcare visits** rather than expecting men to seek them out proactively can subtly increase engagement. This approach, rooted in **choice architecture**, leverages the principle of making the desired behavior (contraceptive consideration) the default option rather than an extra effort.

Additionally, I explored how **feedback loops** reinforce behavioral change. As more men adopt non-hormonal contraceptives, increased visibility and societal normalization drive further acceptance, reducing stigma and promoting long-term adoption. I examined how previous public health campaigns successfully altered behaviors, drawing parallels to how similar strategies could be applied to increase male contraceptive uptake.

By integrating behavioral economics principles, including **incentive framing, strategic defaults, and reinforcing feedback loops**, I demonstrated a comprehensive and actionable approach to behavior modification in the context of contraceptive responsibility, aligning well with a strong **4-level application** of **#shapingbehavior**.

HC: #interventionalstudy

Description of the HC from the course syllabus: Design and interpret experimental studies by manipulating independent variables while controlling extraneous factors to establish causal relationships.

What is a "4" level application of this HC as described in the course? A 4-level application requires a well-structured experimental design with clear definitions of independent and dependent variables, controls, and rigorous justification for methodological choices. It also involves evaluating limitations and real-world applicability.

What would be a "4" level application of this HC in THIS project? In this paper, a strong 4-level application of **#interventionalstudy** would involve analyzing the experimental setups of contraceptive trials, detailing their methodological frameworks, and critiquing their effectiveness. This includes assessing study variables such as dosage levels, administration routes, and primary endpoints while evaluating how well these designs control for confounding factors.

Where is this HC applied in your project? This HC is applied in **the Gel section** and **the RAR Antagonist Experiments section**, where I examine the interventional study designs used to evaluate YCT-529 and related compounds.

How have I applied this HC in this project? I applied **#interventionalstudy** by analyzing clinical and preclinical studies on RAR antagonists, including BMS-189453, where I examined how different dosing regimens influenced spermatogenesis inhibition. I explored how study designs varied in their use of single-dose versus repeated administration and how fertility recovery was measured post-treatment.

In the **Gel section**, I evaluated the Phase IIb trial of a contraceptive gel, detailing how investigators defined primary endpoints such as sperm concentration reduction and secondary outcomes like systemic safety. I highlighted how placebo-controlled randomization minimizes bias and discussed ethical considerations in participant selection.

Beyond analyzing individual studies, I also compared different experimental frameworks, assessing how toxicology screenings and pharmacokinetic evaluations informed dose-response relationships. This thorough approach demonstrates a clear **4-level** application by showcasing an in-depth evaluation of interventional study methodologies and their broader implications for male contraceptive development.

HC: #evidencebased

Description of the HC from the course syllabus: Identify and appropriately structure the information needed to support an argument effectively. This HC involves selecting credible sources, structuring evidence logically, and integrating multiple forms of data to strengthen claims.

What is a "4" level application of this HC as described in the course? A **4-level application** requires not just citing sources but critically evaluating them, ensuring they are well-integrated into the argument. This means demonstrating a clear rationale for why each piece of evidence is relevant, comparing conflicting data where necessary, and presenting evidence in a structured and persuasive manner.

What would be a "4" level application of this HC in THIS project? In this project, a **4-level application** of **#evidencebased** would involve weaving together molecular, genetic, and interventional study data to support claims about the efficacy of RAR inhibition in male contraception. Strong applications would synthesize results across disciplines, from pharmacology to endocrinology, ensuring that each claim is justified through diverse, high-quality evidence.

Where is this HC applied in your project? This HC is extensively applied in the **Contraceptive Efficacy** section, where I evaluate clinical trials, and in the **RAR Inhibition and the Creation of YCT-529** section, where I integrate molecular analyses and receptor interactions.

How have I applied this HC in this project? I applied **#evidencebased** by systematically integrating multiple forms of evidence to construct a scientifically rigorous argument. In the **Contraceptive Efficacy** section, I critically analyzed the interventional study by Ilani et al., discussing its methodology, randomization, treatment regimens, and measured outcomes. I assessed the study's limitations, ensuring that readers could contextualize the findings within the broader contraceptive research landscape.

In the **RAR Inhibition and the Creation of YCT-529** section, I used structural analyses to illustrate how YCT-529 selectively binds to RAR-α, inhibiting its activity and disrupting spermatogenesis. I provided molecular diagrams and referenced structural biology studies to validate the antagonist's mechanism of action.

Furthermore, in discussing **retinoic acid's role in spermatogenesis**, I incorporated genetic data, emphasizing how RA regulates key genes involved in germ cell differentiation. This involved synthesizing studies on gene expression, protein interactions, and pharmacokinetics to paint a comprehensive picture of YCT-529's function.

By employing a multi-tiered evidentiary approach—ranging from **clinical trials and molecular pharmacology** to **genetic regulation**—I ensured that every claim was substantiated, making this a strong **4-level application** of **#evidencebased**.

HC: #gapanalysis

Description of the HC from the course syllabus: Identify and evaluate whether there are suitable existing solutions to a problem or whether a creative new solution is required. A strong application requires assessing the limitations of current solutions, determining gaps in their effectiveness, and justifying the need for a novel approach.

What is a "4" level application of this HC as described in the course? A **4-level application** critically examines existing solutions, identifying weaknesses and systematically evaluating their feasibility. This includes discussing whether modifications to current solutions could work or if a completely new intervention is necessary. The analysis must be well-supported, logically structured, and clearly justify the identified gap.

What would be a "4" level application of this HC in THIS project? In this project, a **4-level application** of **#gapanalysis** involves evaluating the shortcomings of existing male contraceptives, such as condoms, vasectomies, and hormonal methods, and demonstrating why non-hormonal alternatives like YCT-529 are needed. This includes highlighting the limitations of vasectomies' permanence, the inconsistent efficacy of condoms, and the adverse side effects of hormonal contraceptives.

Where is this HC applied in your project? This HC is applied in the **Background Information - Contraception** section, where I examine the drawbacks of current contraceptives, and in **Chapter One: Current State of Understanding - Hormonal Male Contraceptives**, where I assess the adverse effects of male hormonal options.

How have I applied this HC in this project? I applied **#gapanalysis** by systematically critiquing existing male contraceptive methods and demonstrating their shortcomings. In the **Background Information** section, I analyzed how condoms are highly user-dependent and prone to failure, while vasectomies are invasive and permanent, limiting male contraceptive choices. I also discussed the shortcomings of emerging solutions like contraceptive gels, which face adherence challenges.

In **Chapter One**, I examined hormonal male contraceptives, detailing their associated side effects such as mood swings, weight gain, and reduced libido, which significantly impact user compliance. By comparing these challenges to the relative safety and reversibility of YCT-529, I illustrated why a non-hormonal alternative is necessary.

Furthermore, I evaluated past research on RAR antagonists, highlighting how prior compounds like BMS-189453 showed potential but failed due to toxicity concerns. This analysis established the gap YCT-529 fills, demonstrating how its refined selectivity for RAR-α minimizes toxicity while maintaining contraceptive efficacy.

By conducting a thorough gap analysis across multiple domains—contraceptive efficacy, user adherence, and pharmacological safety—I built a compelling case for YCT-529's role in addressing unmet needs. This structured, evidence-backed approach exemplifies a strong **4-level application** of **#gapanalysis**.

HC: #communicationdesign

Description of the HC from the course syllabus: Apply principles of perception and cognition in oral and multimedia presentations and in design. Effective communication design optimizes information delivery by structuring visual and textual elements in a way that enhances comprehension and engagement.

What is a "4" level application of this HC? A **4-level** application demonstrates a deliberate and strategic use of visual and structural design principles to enhance information processing. This includes integrating graphics, figures, and slides that adhere to cognitive design principles such as **limited capacity, compatibility, informative change, and redundancy reduction**. The application should show clear intent in using design elements to aid comprehension and avoid unnecessary complexity.

What would be a "4" level application of this HC in THIS project? A strong application in this project involves optimizing the visual and textual presentation of complex biochemical and pharmacological data through structured graphical elements. This includes **graphical abstracts, research posters, and well-annotated figures** that allow readers to grasp core findings efficiently. Additionally, using principles of **contrast, alignment, and hierarchy** in designing tables and visual elements ensures clarity and accessibility.

Where is this HC applied in your project? This HC is applied in both papers: - In the **Review Paper**, the **graphical abstract** visually condenses the main findings of YCT-529's mechanism and pharmacology. - In the **Research Paper**, while the graphical abstract is pending, key figures and tables adhere to **principles of effective communication design**. - **Research posters** created for both papers summarize extensive data concisely, making them digestible for both academic and general audiences.

How have I applied this HC in this project? I deeply integrated **communication design** principles by ensuring that all visuals—**graphical abstracts, figures, and research posters**—enhanced comprehension rather than merely supplementing text.

1. **Graphical Abstract in the Review Paper**: I structured a concise, visually engaging summary of YCT-529's pharmacodynamics and clinical implications. The abstract conveys the molecular interactions, pharmacokinetics, and key study findings at a glance, catering to **visual learners** who process information more effectively through diagrams rather than text-heavy explanations.

2. **Research Posters for Both Papers**: Research posters serve as a compact yet detailed representation of findings. I employed **minimal text, clear headings, high-contrast colors, and figure-first design** to ensure that key insights—such as drug efficacy, selectivity, and receptor binding data—are immediately understandable. The use of **limited capacity principles** prevented cognitive overload, allowing readers to absorb information efficiently.

3. **Figures and Visual Annotations**: Throughout both papers, I carefully designed figures with **compatibility and redundancy reduction** in mind. For instance, in the Review Paper, **binding affinity comparisons between RAR-α, RAR-β, and RAR-γ antagonists** were structured in a visually intuitive table with clear legends. Instead of relying solely on text, the figures themselves conveyed essential patterns in receptor selectivity.

Why is this a 4-level application? By employing **graphical abstracts, visually optimized research posters, and cognitively efficient figure designs**, I ensured that my work remains accessible across different learning preferences. The deliberate use of **limited capacity and compatibility principles** in structuring visuals strengthens clarity while maintaining scientific rigor. These applications demonstrate a deep, intentional engagement with **#communicationdesign**, enhancing both readability and academic impact.

HC: #plausibility

Description of the HC from the course syllabus: Evaluate whether hypotheses are based on plausible premises or assumptions. A strong application ensures hypotheses align with established scientific knowledge, logical reasoning, and empirical data, avoiding unfounded speculation.

What is a "4" level application of this HC as described in the course? A **4-level application** involves thoroughly justifying the assumptions behind a hypothesis,

demonstrating consistency with scientific literature, and providing empirical support. This requires evaluating alternative explanations and ensuring logical coherence between molecular mechanisms and observed outcomes.

What would be a "4" level application of this HC in THIS project? In this project, a **4-level application** of **#plausibility** entails validating the hypothesis that RAR-α inhibition by YCT-529 effectively disrupts spermatogenesis. This includes confirming the necessity of RAR- in germ cell development and ensuring YCT-529's selectivity and efficacy through molecular and pharmacokinetic studies.

Where is this HC applied in your project? This HC is applied in **Retinoic Acid and Spermatogenesis** and **RAR Antagonism in Male Contraception**, where I evaluate RAR-α inhibition's mechanistic plausibility and analyze YCT-529's structural specificity and biological effects.

How have I applied this HC in this project? I applied **#plausibility** by critically assessing the theoretical and empirical basis of YCT-529's contraceptive function. In **Retinoic Acid and Spermatogenesis**, I demonstrated that RAR-α plays an essential role in germ cell differentiation, citing knockout studies where its inhibition led to failed spermatogenesis. This confirmed that disrupting this receptor is a biologically viable contraceptive strategy.

In **RAR Antagonism in Male Contraception**, I analyzed YCT-529's chemical features, particularly its chromene core, pyrrole ring, and benzoic acid moiety, which contribute to its selective binding to RAR-α. I compared its pharmacokinetic profile and efficacy data (99% contraception rate in murine models), reinforcing that its hypothesized function aligns with experimental results.

Additionally, I evaluated alternative pathways that could influence YCT-529's effects, such as potential off-target interactions with other nuclear receptors. By cross-referencing structural and binding affinity data, I ruled out major confounders, ensuring that YCT-529's observed contraceptive mechanism is the most plausible explanation.

Through rigorous evaluation of assumptions, integration of molecular and empirical evidence, and elimination of alternative hypotheses, I demonstrated a **4-level** application of **#plausibility**, ensuring YCT-529's mechanistic hypothesis is both scientifically sound and empirically validated.

HC: #testability

Description of the HC from the course syllabus: Evaluate whether hypotheses lead to testable predictions. A well-applied case of **#testability** generates measurable predictions and ensures that hypotheses can be rigorously evaluated using empirical methods.

What is a "4" level application of this HC as described in the course? A **4-level application** involves generating multiple independent predictions that can support or refute a hypothesis, ensuring that testing methodologies are feasible and results are interpretable. It requires designing controlled conditions and justifying how confounding variables are minimized.

What would be a "4" level application of this HC in THIS project? A **4-level application** in this project entails defining testable endpoints for YCT-529's efficacy in spermatogenesis inhibition and pharmacokinetic validation. This includes specifying quantifiable measures such as sperm count reduction, RAR-α binding affinity, and metabolic clearance rates, ensuring that predictions are empirically verifiable.

Where is this HC applied in your project? This HC is applied in **Experimental Validation of Spermatogenesis Inhibition** and **Clinical Development and Phase 1 Trials**, where I outline measurable predictions and controlled study designs for evaluating YCT-529's pharmacodynamics and safety.

How have I applied this HC in this project? I applied **#testability** by defining clear experimental predictions and validating them through structured methodologies. In **Experimental Validation of Spermatogenesis Inhibition**, I detailed how YCT-529's effect on spermatogenesis was assessed using murine models, specifying quantifiable endpoints such as sperm count reduction, motility impairment, and germ cell apoptosis. These metrics established direct, measurable outcomes linking RAR-α antagonism to fertility suppression.

In **Clinical Development and Phase 1 Trials**, I evaluated YCT-529's pharmacokinetics through a **randomized, double-blind, placebo-controlled** study design. By incorporating dose-escalation cohorts and measuring plasma drug concentrations, metabolic half-life, and adverse event frequency, I ensured that trial methodologies were structured for robust hypothesis testing. The inclusion of placebo groups and control arms further strengthened the validity of causal inferences.

Additionally, I justified the practicality of testing predictions by addressing ethical constraints and feasibility. For example, while direct human spermatogenesis inhibition trials require long-term follow-up, short-term markers such as testosterone levels and LH/FSH suppression were used as early indicators of drug efficacy. This ensured that the experimental design balanced scientific rigor with ethical responsibility.

By integrating precise endpoints, controlled methodologies, and feasibility assessments, I demonstrated a **4-level** application of **#testability**, ensuring that all hypotheses regarding YCT-529's mechanism, pharmacokinetics, and efficacy were empirically verifiable.

HC: #dataviz

Description of the HC from the course syllabus: Interpret, analyze, and create data visualizations. Effective data visualization enhances the clarity of complex data, allowing for more intuitive interpretation and communication of key trends, patterns, and relationships.

What is a "4" level application of this HC as described in the course? A **4-level application** requires selecting and designing appropriate visualizations that accurately depict trends, relationships, and key patterns within the data. The visualizations should enhance the argument, be well-labeled, and facilitate clear, evidence-based analysis.

What would be a "4" level application of this HC in THIS project? A **4-level application** in this project involves using data visualization to represent biochemical pathways, receptor interactions, and experimental outcomes. Figures should be selected and formatted to provide clear insights into molecular mechanisms, compound efficacy, and pharmacokinetic trends.

Where is this HC applied in your project? This HC is applied in both the research and review papers, particularly in: - **Biochemical Pathways of Retinoic Acid Signaling**, where schematic representations clarify RA's role in gene regulation and spermatogenesis. - **Molecular Structure and Binding Affinities**, where data visualizations illustrate the structural differences between YCT-529 and other RAR antagonists. - **Pharmacokinetic and Preclinical Data**, where line graphs and dose-response curves depict YCT-529's efficacy in preclinical models.

How have I applied this HC in this project? I employed **#dataviz** by integrating clear, precise visualizations to enhance comprehension of complex molecular and pharmacological data. In the **Biochemical Pathways of Retinoic Acid Signaling** section, I included schematic illustrations that mapped key interactions between RA, RAR-α, and downstream gene regulators. These visuals simplified complex regulatory mechanisms, making them more accessible to readers.

In the **Molecular Structure and Binding Affinities** section, I presented a comparative figure depicting the structures of YCT-529, chromene-based, and tetrahydronaphthalene - derived RAR antagonists. By integrating binding affinity values (K_i) alongside molecular diagrams, I demonstrated the structure-activity relationship that underpins YCT-529's specificity for RAR-α. This approach allowed for an immediate visual comparison of how different chemical modifications influence receptor binding.

Additionally, in the **Pharmacokinetic and Preclinical Data** sections, I used dose-response curves and line graphs to depict YCT-529's impact on spermatogenesis inhibition in murine models. By incorporating appropriate axis labels, legends, and statistical markers, I ensured that the visualizations conveyed key findings effectively without ambiguity.

Each visualization was carefully selected and formatted to support the paper's analytical framework, ensuring that molecular, biochemical, and pharmacokinetic trends were communicated with clarity. This application meets the **4-level** standard by integrating well-structured, informative figures that enhance argumentation and facilitate deeper insight into YCT-529's pharmacological potential.

HC: #sourcequality

Description of the HC from the course syllabus: Distinguish between categories and types of information to determine source quality. Evaluating sources involves assessing their currency, relevance, authority, accuracy, and purpose (CRAAP criteria) to ensure credibility in academic and professional work.

What is a "4" level application of this HC as described in the course? A **4-level application** involves rigorously evaluating sources using well-defined criteria, prioritizing peer-reviewed research, and balancing historical and contemporary literature. A strong application includes assessing bias, corroborating findings across multiple sources, and ensuring that cited works directly support claims.

What would be a "4" level application of this HC in THIS project? A **4-level application** in this project requires selecting high-quality sources from authoritative

journals, critically analyzing their methodology, and cross-referencing key findings. It also involves balancing foundational studies with recent advances in the field to ensure an accurate and comprehensive review.

Where is this HC applied in your project? This HC is applied throughout both the research and review papers, particularly in: - **Background Information on Contraceptive Methods**, where peer-reviewed studies are used to compare male and female contraceptives. - **RAR Antagonists and Spermatogenesis**, where sources such as **Noman et al. (2020)** and **Bansode et al. (2023)** provide mechanistic insights into YCT-529. - **Pharmacokinetic and Toxicological Evaluations**, where cross-referencing between animal model studies and clinical trial data ensures validity.

How have I applied this HC in this project? I applied **#sourcequality** by critically selecting and evaluating sources based on the **CRAAP** criteria—currency, relevance, authority, accuracy, and purpose. In the **Background Information on Contraceptive Methods** section, I analyzed foundational works such as **Russell et al. (1993)** for historical context while incorporating recent studies like **Bansode et al. (2023)** to present the latest advancements in YCT-529 research. This ensured a balanced perspective that integrated both established principles and emerging insights.

In the **RAR Antagonists and Spermatogenesis** section, I prioritized peer-reviewed articles from high-impact journals, such as **Biology of Reproduction** and **Nature Reviews Endocrinology**, to substantiate claims regarding retinoic acid receptor inhibition. Each study was assessed for methodological rigor, sample size, and statistical validity to ensure that conclusions were well-supported.

Additionally, I cross-verified key findings by comparing multiple sources. For example, YCT-529's selectivity for RAR- was corroborated across several studies, ensuring that the reported binding affinities and inhibition profiles were consistent. By excluding sources with potential biases—such as industry-sponsored reports without independent validation—I upheld high standards of academic integrity.

This application meets the **4-level** standard by integrating well-vetted sources, critically evaluating their reliability, and constructing a robust, evidence-based narrative throughout both papers.

HC: #composition

Description of the HC from the course syllabus: Communicate with a clear and precise style. Effective composition prioritizes conciseness, clarity, and audience engagement by eliminating unnecessary complexity, avoiding passive voice, and structuring

content for coherence and readability.

What is a "4" level application of this HC as described in the course? A **4-level application** demonstrates a clear, well-organized style that balances conciseness with depth. This includes maintaining parsimony while explaining complex ideas, tailoring communication to the audience, and structuring the document for readability without sacrificing essential details.

What would be a "4" level application of this HC in THIS project? A **4-level application** in this project involved strategically organizing both the review and research papers to balance detail and readability. The main review paper was kept at approximately **5,000 words**, and the research paper at **3,500 words**, while additional technical content, methodological discussions, and extended analyses were placed in the appendices. This ensured that the core paper remained accessible while maintaining the depth necessary for a comprehensive discussion.

Where is this HC applied in your project? This HC is applied throughout both papers, particularly in: - **Chemical Composition and Structure of YCT-529**, where molecular details are communicated with precision, avoiding unnecessary jargon. - **Medicinal Chemistry of RAR Inhibitors**, where the evolution of RAR ligands is explained succinctly while maintaining scientific rigor. - **Appendices**, where extended discussions, additional data, and supplementary explanations were placed to enhance clarity without overburdening the main text.

How have I applied this HC in this project? I applied **#composition** by maintaining conciseness without compromising technical accuracy. In the **Chemical Composition and Structure of YCT-529** section, I described the chromene core, pyrrole ring, and benzoic acid moiety with direct explanations, ensuring that complex chemical properties were conveyed efficiently. To avoid overwhelming the reader, I structured paragraphs logically and used precise terminology to enhance readability.

In the **Medicinal Chemistry of RAR Inhibitors** section, I summarized the evolution of RAR ligands in a structured and clear manner, ensuring that key developments were highlighted without excessive detail. Additionally, I placed extensive discussions on computational docking studies and receptor interactions in the appendices, ensuring that the main paper remained focused while still providing in-depth insights for readers seeking additional information.

By structuring both papers efficiently, using clear and concise language, and strategically placing extended content in appendices, I demonstrated a **4-level** application of **#composition**, making the work accessible yet rigorous.

HC: #professionalism

Description of the HC from the course syllabus: Follow established guidelines to present yourself and your work products professionally. This includes adhering to formatting conventions, ensuring clarity and consistency, and maintaining appropriate tone and structure.

What is a "4" level application of this HC? A 4-level application demonstrates strict adherence to academic and professional standards, including proper formatting, accurate citations, clear organization, and polished language. Work is free from avoidable errors and meets the expectations of a scholarly audience.

What would be a "4" level application of this HC in THIS project? A strong application involves maintaining formal structure, using **LaTeX** for formatting, and ensuring figures, tables, and references are integrated clearly. Citations must follow the **Vancouver style**, and the writing must be precise, avoiding redundancy while upholding clarity and readability.

Where is this HC applied in your project? This HC is evident throughout the paper, particularly in the structured integration of figures (e.g., Figure 5, Figure 7), adherence to **Vancouver citation style**, and the polished presentation of research findings.

How have I applied this HC in this project? I ensured consistency in formatting using **LaTeX**, applied Vancouver-style citations accurately, and maintained a professional tone. The document is free from typographical or grammatical errors, with sections clearly delineated for readability. Figures and tables were formatted with proper captions and in-text references, ensuring clarity and accessibility. These efforts collectively enhance the credibility and scholarly rigor of the work.